



The Fogarty International Center MISMS Newsletter

Fall 2009

MISMS Africa Meeting – April 21-25, 2009. Dakar, Senegal

The Multinational Influenza Seasonal Mortality Study (MISMS) is an international collaborative effort led by the Fogarty International Center – Division of International Epidemiology and Population Studies (FIC-DIEPS) to analyze disease patterns associated with influenza virus circulation. Following the success of previous regional meetings in South America (February 2007), Asia (August 2007), and Europe (September 2008), the [2009 MISMS Africa Meeting](#) was held in April 2009 in Dakar, Senegal. Participants of the MISMS Africa meeting included influenza epidemiologists, virologists, computational biologists, and public health officials. The meeting was co-hosted by the Institut Pasteur de Dakar and was held at the Meridien President Hotel and Conference Center, Pointe des Almadies, Dakar, Senegal.

The first two days of the meeting consisted of presentations highlighting MISMS's research results and the progress that has been made in characterizing influenza epidemiology, specifically in Africa. Over 50 participants from universities and veterinary and public health institutions throughout Africa, Europe, and the United States attended the meeting. Topics addressed included the impact of influenza in Africa; the ecology and surveillance of highly-pathogenic avian influenza viruses, seasonal influenza viruses, influenza-like illness, and severe acute respiratory illnesses; the genetic and antigenic evolution of influenza viruses, antiviral resistance, and vaccines; the emergence of antiviral resistance; and options for future collaborations. Speakers included National Institutes of Health (NIH) staff, scientists from the US Centers for Disease Control and Prevention (CDC), and researchers from various academic institutions and foreign public health agencies. Participants were actively engaged in the

SAVE THE DATE!
MISMS Australia Meeting and Workshop
 Melbourne, Australia
 March 15 – 19, 2010

The **MISMS Australia Meeting & Workshop** will feature research describing regional and national patterns in disease burden and evolutionary dynamics of influenza viruses. Following the meeting, a technical workshop will be held that will evaluate effective methodological approaches to analyzing vital statistics and virological, genomic, and economic data, specifically as they pertain to influenza disease burden and policy development. All are invited to attend the general meeting and workshop. Visit <http://www.origem.info/misms/program.php> for up-to-date info!



Participants in MISMS Africa Meeting, April 2009
Dakar, Senegal



presentations, debating a wide variety of influenza-related issues, including the issue of data sharing for common benefit. NIH-funded resources aimed at improving the availability of influenza genomic sequences, such as the Influenza Genome Sequencing Project and related information were presented, and the procedures on how to benefit from these resources were explained in great detail.

Following the presentations, a 2½-day long workshop was held during which participants received hands-on technical training in the analysis of influenza morbidity and mortality data, as well as influenza genomic data. NIH staff assisted individuals and small groups with data cleaning, formatting, and analysis and demonstrated these techniques using sample data from programs prepared at the NIH. The workshop provided participants with a unique networking opportunity that enabled scientists from different countries to share their experiences and knowledge and to establish relationships that will yield better regional and international collaborations.

The overall feedback of the MISMS Africa meeting was positive. Among those elements that participants found to be the most valuable were the collegial and interactive nature of the workshop and the opportunity to build connections with other African scientists and international experts, including many from the NIH. Participants highlighted the need for further influenza research training and collaboration in Africa. The timing of the workshop was fortuitous, as many attendees returned home in time to participate in national preparedness activities targeting the nascent A/H1N1 pandemic.

MISMS Influenza Dynamics and Evolutionary Analysis (IDEA) Workshop – April 24-26, 2009. Bethesda, MD

Between June 24 and 26, 2009, the Fogarty International Center (FIC) hosted the inaugural [Influenza Dynamics and Evolutionary Analysis \(IDEA\) workshop](#) at the NIH Headquarters in Bethesda, MD. The workshop brought together researchers from all six major continents, including virologists, evolutionary biologists, and representatives from the public and private sectors. The first day and a half of the workshop consisted of oral presentations by participants on a wide range of topics relating to the study of influenza virus evolution, including US and global surveillance, bioinformatics, phylogenetics, antigenic cartography, database generation, and genomic sequencing. For the remainder of the workshop, Drs. Eddie Holmes, Andrew Rambaut, and Derek Smith led an interactive demonstration of innovative epidemiological and phylogenetic methodologies and worked with participants to analyze their own virological data. We were incredibly pleased by how enthusiastically the virologists grasped the power of phylogenetics to analyze viral sequence data and by the new collaborations that were forged over the three day meeting.



Participants in MISMS IDEA Meeting, June 2009
Washington, DC



Guest Researcher Spotlight

The Fogarty International Center's MISMS program utilizes a number of collaborative mechanisms, including the support of visiting fellows who perform research at the NIH Headquarters in Bethesda, Maryland. Recent guest researchers have come from France, Italy, Taiwan, Brazil, Japan, South Korea, South Africa, Australia, Portugal, and the US. Here we spotlight researchers Nesli Saglanmak and Alice Fusaro, both of whom visited FIC in 2009.

Nesli Saglanmak, Roskilde University, Roskilde, Denmark

Currently pursuing a PhD in applied mathematics from Roskilde University in Denmark, Nesli's experience at FIC helped guide her current interests in influenza epidemiology. During her six-month stay at FIC, she worked on age-related influenza mortality in the years surrounding the 1918 pandemic. Using historical data from Copenhagen, she focused her research on the shift in age structure during and after the pandemic. Nesli will present her findings in December at the Epidemics² conference in Greece and hopes to publish her findings in a peer-reviewed journal soon thereafter.

Nesli's work on modeling physiological systems helped her transition into her current graduate program. Her work with FIC gave her a unique "experience working in a major public health research facility." Looking toward the future, Nesli hopes to continue researching mathematical models of epidemics.



The diverse interests and experiences of FIC's researchers helped create a unique collaborating environment that Nesli found both rewarding and educational. Despite working so far from her home in Denmark, she found little to miss because Washington, DC had so much to offer. Finding her colleagues both friendly and inviting, she always felt as welcome part of the group. Still, despite her many positive experiences at FIC, she was admittedly not ready for the weather in DC. "I missed the Danish wind during the very humid summertime in DC."

Alice Fusaro, Istituto Zooprofilattico Sperimentale delle Venezie, Padova, Italy

After graduating with a master's degree in biotechnology from the University of Padova in 2006, Alice joined the Istituto Zooprofilattico Sperimentale delle Venezie (IZSve) in Padua, Italy, a veterinary public health institute that conducts laboratory controls and research activities in three main areas: animal health and welfare, food safety, and environmental protection. IZSve is also an OIE/FAO international reference laboratory for Newcastle disease and avian influenza. After joining IZSve, Alice became involved with the phylogenetic and evolutionary analysis of these two diseases. In 2007, she trained with a group of researchers who focused on genetic sequencing at the J. Craig Venter Institute, and in 2008, she completed coursework on computational biology at the Universities of Cambridge (UK) and Torino (Italy). In September 2008, she attended the MISMS Europe Meeting in Vilamoura, Portugal, where she was invited to spend five weeks analyzing avian influenza data at FIC.



While at FIC, Alice focused her research on the evolution of Highly Pathogenic Avian Influenza (HPAI) A/H5N1 in Nigeria, a project that included the analysis of spatial migration, genetic diversity, and evolutionary rates. Under the guidance of Martha Nelson, PhD, Eddie Holmes, PhD, and Katharine Sturm-Ramirez, PhD, she learned to use analytical software like PAUP* and MacClade, enabling her to analyze relevant data. During her time in the US, Alice had the opportunity to collaborate with FIC researchers to analyze epidemiologic data and interpret corresponding results. Collaborations between FIC and IZSve are ongoing, and Alice hopes to publish her research findings soon.

Some highlights of Alice's stay in the US include going to the movies with colleagues, spending time with Martha's family, traveling to New York City for Easter, and attending her first baseball game. Attending the June 2009 IDEA workshop in Washington DC, she found it to be "another great opportunity to expand [her] knowledge on the phylogenetic and evolutionary analysis of influenza viruses."

Alice has authored or coauthored ten publications thus far, and this September, she taught a one-week course on genetic sequencing and phylogenetic analysis to trainers from Chile, Brazil, Argentina, Paraguay, and Uruguay. Alice hopes to continue working closely with FIC on phylogenetic analyses. By continuing to publish, she seeks to help basic science researchers in low-resource areas improve their knowledge of the sequencing and evolutionary analysis of influenza and other viruses. Her research interests have helped mold her perspective on global health: "[T]he most important public health issue is the understanding, prevention, and control of zoonotic diseases and food safety. Ensuring safe food is paramount for the protection of human health and the enhancement of people's quality of life."

Focus: PLoS Currents

"PLOS Currents: Influenza" (<http://www.plos.org/cms/node/481>) is a web-based scientific publication that seeks to rapidly disseminate data and ideas in the realm of influenza research. MISMS researchers, and the greater NIH research community, have been instrumental in helping the concept of PLoS Currents materialize. FIC researchers Eddie Holmes, Mark Miller, and Cecile Viboud are among the group of international influenza experts that moderates this collaborative venture.

Among the first contributions to PLoS Currents are studies that address important aspects of the ongoing swine-origin influenza virus (H1N1pdm) pandemic. These contributions include a paper by Chowell and colleagues that utilizes case study data from Mexico to illustrate how H1N1pdm can be controlled with limited vaccine supplies. Another submission by Rambaut and Holmes uses the rapidly growing database of publicly-available influenza virus genome sequences to investigate the molecular epidemiology and evolution of H1N1pdm. Both studies are highlighted later in this newsletter.

A broad range of submissions is considered for publication in PLoS Currents, including observations, ideas, data, and even complete manuscripts. Works are screened rapidly by a group of expert moderators to exclude unsuitable material; however, these submissions do not receive the in-depth peer-review required by the PLoS print journals. Accordingly, PLoS encourages authors to submit their PLoS Currents contributions, or work that synthesizes ideas and information from PLoS Currents, to one of PLoS's peer-reviewed research journals, where they will then enter a standardized review process.

Although PLoS Currents was created in response by the current H1N1 pandemic, the website also includes research on all influenza virus subtypes. It is a place to share results and ideas immediately while ensuring that they will be permanently archived and citable for other investigators. Researchers submitting results will also be contributing to the global response effort to the recent emergence of H1N1 influenza and the urgent and ever-present public health threat posed by influenza viruses.



Study Highlights

MISMS collaborators published a breadth of articles on influenza viruses over the years. Recent articles focus on topics as diverse as the influenza phylogenetics, disease burden, antigenic mapping, and pandemic policy. In response to the 2009 A/H1N1 influenza, the MISMS network has been involved in multiple ventures that proactively address and directly measure the impact of this pandemic.

DISEASE BURDEN OF H1N1

Chowell G, Bertozzi S, Colchero M, Lopez-Gatell H, Alpuche-Aranda C, Hernandez M, Miller MA (Aug 13, 2009) Severe Respiratory Disease Concurrent with the Circulation of H1N1 Influenza. *N Engl J Med.* 361: 674-9.

Background: In the spring of 2009, an outbreak of severe pneumonia was reported in conjunction with the concurrent isolation of a novel swine-origin influenza A (H1N1) virus (S-OIV), widely known as swine flu, in Mexico. Influenza A (H1N1) subtype viruses have rarely predominated since the 1957 pandemic. The analysis of epidemic pneumonia in the absence of routine diagnostic tests can provide information about risk factors for severe disease from this virus and prospects for its control.

Methods: From March 24 to April 29, 2009, a total of 2155 cases of severe pneumonia, involving 821 hospitalizations and 100 deaths, were reported to the Mexican MOH. During this period, of the 8817 nasopharyngeal specimens that were submitted to the National Epidemiological Reference Laboratory, 2582 were positive for S-OIV. We compared the age distribution of patients who were reported to have severe pneumonia with that during recent influenza epidemics to document an age shift in rates of death and illness.

Results: During the study period, 87% of deaths and 71% of cases of severe pneumonia involved patients between the ages of 5 and 59 years, as compared with average rates of 17% and 32%, respectively, in that age group during the referent periods. Features of this epidemic were similar to those of past influenza pandemics in that circulation of the new influenza virus was associated with an off-season wave of disease affecting a younger population.

Conclusions: During the early phase of this influenza pandemic, there was a sudden increase in the rate of severe pneumonia and a shift in the age distribution of patients with such illness, which was reminiscent of past pandemics and suggested relative protection for persons who were exposed to H1N1 strains during childhood before the 1957 pandemic. If resources or vaccine supplies are limited, these findings suggest a rationale for focusing prevention efforts on younger populations.

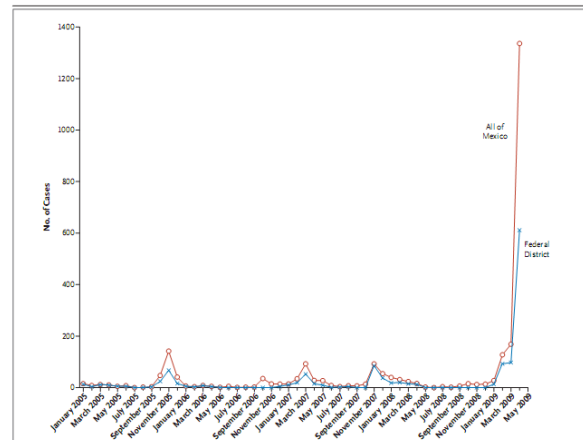


Figure 1. Time Series of Confirmed Cases of Influenza in the Federal District and in All of Mexico, According to Month (January 2005–April 2009). Data are from the National Epidemiological Reference Laboratory.

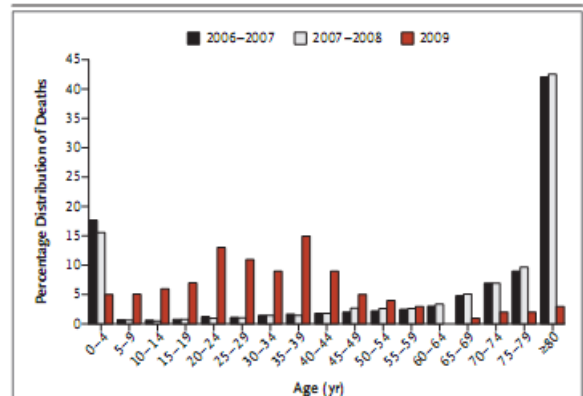


Figure 2. Percentage Distribution of Deaths from Severe Pneumonia during the 2009 Study Period, as Compared with Influenza Seasons from 2006 through 2008, in Mexico, According to Age Group.

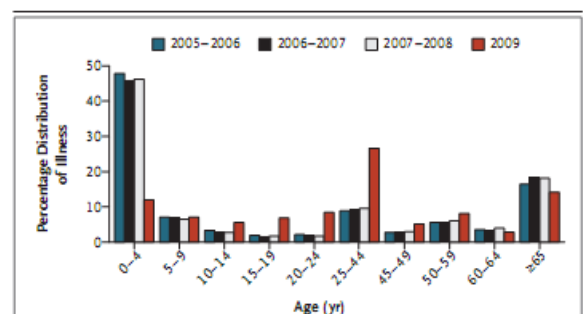


Figure 3. Percentage Distribution of Illness from Severe Pneumonia during the 2009 Study Period, as Compared with Influenza Seasons from 2005 through 2008, in Mexico, According to Age Group.



INFLUENZA VIRUS EVOLUTIONARY DYNAMICS AND PATTERNS

Rambaut A, Holmes E. The early molecular epidemiology of the swine-origin A/H1N1 human influenza pandemic. *PLoS Current: Influenza*. Epub date: August 31, 2009.

Swine-origin pandemic human influenza A virus (H1N1pdm) has spread rapidly around the world since its initial documentation in April 2009. Here we have updated initial estimates of the rate of molecular evolution and estimates of the time of origin of this virus in the human population using the large number of viral sequences made available as part of the public health response to this global pandemic. Currently sampled H1N1pdm sequences share a most recent common ancestor in the first 7 weeks of 2009 with the implication that the virus was transmitting cryptically for up to 3 months prior to recognition. A phylogenetic reconstruction of the data shows that the virus has been circling the globe extensively with multiple introductions into most geographical areas.

Cattoli G, Monne I, Fusaro A, Joannis TM, Lombin LH, Aly MM, Arafa AS, Sturm-Ramirez KM, Couacy-Hymann E, Awuni JA, Batawui KB, Awoume KA, Aplogan GL, Sow A, Ngangnou AC, El Nasri Hamza IM, Gamatié D, Dauphin G, Domenech JM, Capua I (2009) Highly Pathogenic Avian Influenza Virus Subtype H5N1 in Africa: A Comprehensive Phylogenetic Analysis and Molecular Characterization of Isolates. *PLoS ONE*. 4(3): e4842.

Abstract: Highly pathogenic avian influenza virus A/H5N1 was first officially reported in Africa in early 2006. Since the first outbreak in Nigeria, this virus spread rapidly to other African countries. From its emergence to early 2008, 11 African countries experienced A/H5N1 outbreaks in poultry and human cases were also reported in three of these countries. At present, little is known of the epidemiology and molecular evolution of A/H5N1 viruses in Africa. We have generated 494 full gene sequences from 67 African isolates and applied molecular analysis tools to a total of 1,152 A/H5N1 sequences obtained from viruses isolated in Africa,

Europe and the Middle East between 2006 and early 2008. Detailed phylogenetic analyses of the 8 gene viral segments confirmed that 3 distinct sublineages were introduced, which have persisted and spread across the continent over this 2-year period. Additionally, our molecular epidemiological studies highlighted the association between genetic clustering and area of origin in a majority of cases. Molecular signatures unique to strains isolated in selected areas also gave us a clearer picture of the spread of A/H5N1 viruses across the continent. Mutations described as typical of human influenza viruses in the genes coding for internal proteins or associated with host adaptation and increased resistance to antiviral drugs have also been detected in the genes coding for transmembrane proteins. These findings raise concern for the possible human health risk presented by viruses with these genetic properties and highlight the need for increased efforts to monitor the evolution of A/H5N1 viruses across the African continent. They further stress how imperative it is to implement sustainable control strategies to improve animal and public health at a global level.

Table 1. Typical amino acid signature of human influenza viruses observed in the African strains.

Protein	aa position	Predicted aa		Reference	Strains	Mutation
		Avian	Human			
PB2	661	A	T	[34]	A/ck/Ghana/2534/07	A661T
				[34]		
	199	A	S	[9]	A/ck/Egypt/5169-5/07; A/ck/Egypt/5169-6/07	A199S
	627	E	K	[8]	All strains analysed in this study	E627K
PB1-F2	73	K	R	[9]	All strains analysed in this study belonging to IV sublineage	K73E
					A/ck/Egypt/452-1/06; A/ck/Egypt/452-2/07	
	82	L	S	[9]	A/ck/Egypt/5169-1/07; A/ck/Egypt/5169-4/07	L82S
					A/ck/Egypt/5169-5/07; A/Egypt/902786/06	
PA	79	R	Q	[9]	A/ck/Egypt/5169-3/07	R79Q
					A/ck/Nigeria/1071-3/07; A/ck/Nigeria/1071-7/07	
	100	V	A	[7,34]	A/ck/Nigeria/AB13/06; A/ck/Nigeria/AB14/06	V100A
	400	Q/T/S	L	[34]	A/ck/Egypt/1709-3VIR08/07; A/ck/Egypt/2628-2/07	S400L
NP	356	K	R	[9]	A/ck/Burkina Faso/1347-16/06	K356R
				[34]		
	33	V	I	[9]	78/B1 viruses	V33I
					A/ck/Egypt/5169-2/07; A/ck/Egypt/5169-3/07	
M2	109	I	V	[9]	A/ck/Nigeria/1047-8/06	I109V
					A/ck/Sudan/1784-8/06; A/ck/Sudan/1784-7/06	
	55	L	F	[34]	A/ck/Sudan/1784-10/06; A/ck/Sudan/2115-9/06	L55F
					A/ck/Sudan/2115-12/06; A/ck/Sudan/2115-10/06	
NS1				[9]	A/hooded vulture/BurkinaFaso/2/06	
	227	E	R o K (H1N1)	[8]	A/ck/Nigeria/FA4/06; A/ck/Nigeria/FA7/06	E227G
NS2	70	S	G	[9]	A/ck/Nigeria/FA4/06; A/ck/Nigeria/FA7/06	S70G



Nelson MI, Simonsen L, Viboud C, Miller MA, Holmes EC (Jun 2009) The origin and global emergence of adamantane resistant A/H3N2 influenza viruses. *Virology*. 388(2): 270-8.

Abstract: Resistance to the adamantane class of antiviral drugs by human A/H3N2 influenza viruses currently exceeds 90% in the United States and multiple Asian countries. Adamantane resistance is associated with a single amino acid change (S31N) in the M2 protein, which was shown to rapidly disseminate globally in 2005 in association with a genome reassortment event. However, the exact origin of influenza A/H3N2 viruses carrying the S31N mutation has not been characterized, particularly in South-East Asia. We therefore conducted a phylogenetic analysis of the HA, NA, and M1/2 segments of viral isolates collected between 1997 and 2007 from temperate localities in the Northern hemisphere (New York State, United States, 492 isolates) and Southern hemisphere (New Zealand and Australia, 629 isolates) and a subtropical locality in South-East Asia (Hong Kong, 281 isolates). We find that although the S31N mutation was independently introduced at least 11 times, the vast majority of resistant viruses now circulating globally descend from a single introduction that was first detected in the summer of 2003 in Hong Kong. These resistant viruses were continually detected in Hong Kong throughout 2003–2005, acquired a novel HA through reassortment during the first part of 2005, and thereafter spread globally. The emergence and persistence of adamantane resistant viruses in Hong Kong further supports a source-sink model of global influenza virus ecology, in which South-East Asia experiences continuous viral activity and repeatedly seeds epidemics in temperate areas.



Fig. 2. Phylogenetic relationships of the HA gene segment of 231 A/H3N2 influenza viruses sampled from Hong Kong ($n=108$), New York State, USA ($n=72$), New Zealand and Australia ($n=46$) between 1997 and 2007, and 5 influenza vaccine reference strains (A/Sydney/5/1997, A/Wyoming/3/2003 (A/Fujian/411/2002-like), A/California/7/2004, A/Wisconsin/67/2005, and A/Brisbane/10/2007), estimated using an ML method. Labels, shading, and rooting are the same as for Fig. 1, with Introductions #1–#11 referring to those identified in Fig. 1 and influenza vaccine reference strains shaded in dark green. Isolates labeled #7F are associated with Introduction #7 and are A/Fujian/411/2002-like, and isolates labeled #7W are associated with Introduction #7 and are A/Wisconsin/67/2005-like.



PUBLIC HEALTH POLICY

Chowell G, Viboud C, Wang X. Adaptive vaccination strategies to mitigate pandemic influenza: Mexico as a case study. PLoS Currents: Influenza Epub date: August 18, 2008.

In this modeling work, we explore the effectiveness of various age-targeted vaccination strategies to mitigate hospitalization and mortality from pandemic influenza, assuming limited vaccine supplies. We propose a novel adaptive vaccination strategy in which vaccination is initiated during the outbreak and priority groups are identified based on real-time epidemiological data monitoring age-specific risk of hospitalization and death. We apply this strategy to detailed epidemiological and demographic data collected during the recent swine A/H1N1 outbreak in Mexico. We show that the adaptive strategy targeting age groups 6-59 years is the most effective in reducing hospitalizations and deaths, as compared with a more traditional strategy used in the control of seasonal influenza and targeting children under 5 and seniors over 65. Results are robust to a number of assumptions and could provide guidance to many nations facing a recrudescence of A/H1N1v pandemic activity in the fall and likely vaccine shortages.

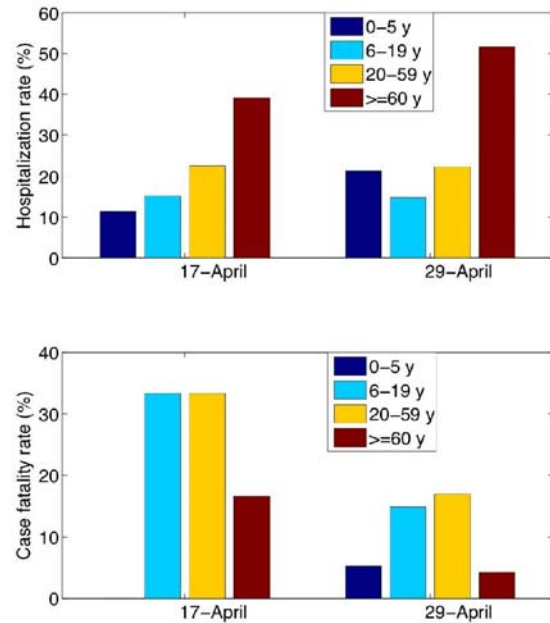


Figure 2: Age-specific rates of hospitalization and death among clinical cases during the S-OIV outbreak in Mexico. Rates are estimated from cumulative morbidity and mortality data provided by the National Surveillance System on April 17 (epidemiological alert) and April 29, 2009 (end of selective reporting of severe pneumonia cases). Hospitalization rate is estimated as the proportion of hospitalizations among pneumonia cases and mortality rate is estimated as the proportion of deaths among hospitalized pneumonia cases.

Miller MA, Viboud C, Balinska M, Simonsen L (Jun 2009) The signature features of influenza pandemics -- implications for policy. N Engl J Med. 360(25): 2595-8.

Vast amounts of time and resources are being invested in planning for the next influenza pandemic, and one may indeed have already begun. Data from past pandemics can provide useful insights for current and future planning. Based on archeo-epidemiologic research, certain "signature features" of three previous influenza pandemics — A/H1N1 from 1918 through 1919, A/H2N2 from 1957 through 1963, and A/H3N2 from 1968 through 1970 — can be clarified, thus informing both national plans for pandemic preparedness and required international collaborations.

These past pandemics were characterized by a shift in the virus subtype, shifts of the highest death rates to younger populations, successive pandemic waves, higher transmissibility than that of seasonal influenza, and differences in impact in different geographic regions. Although influenza pandemics are classically defined by the first of these features, the other four are not frequently considered when developing response plans. This paper outlines how lessons learned from these characteristics can help prioritize national strategies and aid international collaborators in reducing influenza-related mortality.



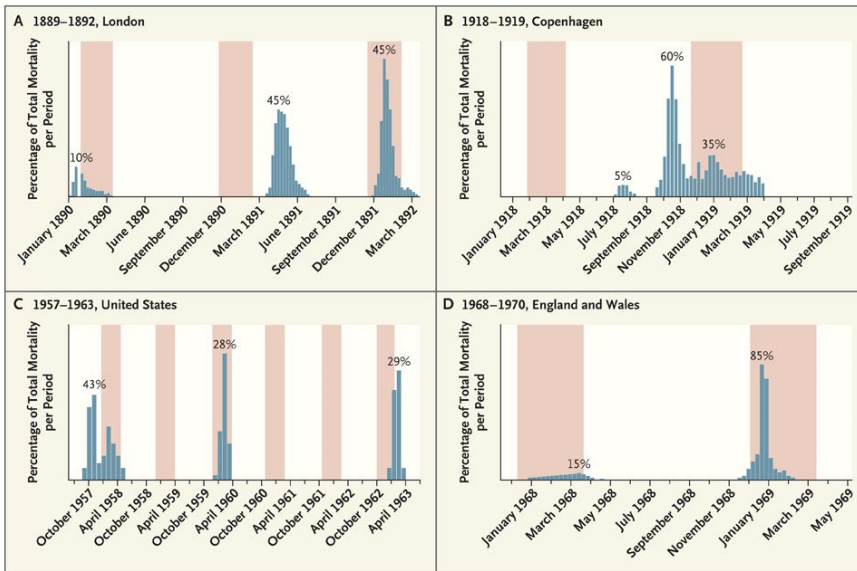


Figure 1: Mortality Distributions and Timing of Waves of Previous Influenza Pandemics- Proportion of the total influenza-associated mortality burden in each wave for each of four previous pandemics is shown above the blue bars. Mortality waves indicate the timing of the deaths during each pandemic. The 1918 pandemic (Panel B) had a mild first wave during the summer, followed by two severe waves the following winter. The 1957 pandemic (Panel C) had three winter waves during the first 5 years. The 1968 pandemic (Panel D) had a mild first wave in Britain, followed by a severe second wave the following winter. The shaded columns indicate normal seasonal patterns of influenza.

de Mello WA, de Paiva TM, Ishida MA, Benega MA, Dos Santos MC, Viboud C, Miller MA, Alonso WJ (Epub Apr 2009) The dilemma of influenza vaccine recommendations when applied to the tropics: the Brazilian case examined under alternative scenarios. PLoS One. 4(4):e5095.

This analysis is an example of how epidemiological studies and partnerships supported by MISMS can be translated into practical public health policies. Developed in collaboration with Brazilian laboratories that participate in the WHO Global Influenza Surveillance Network, the study measured the effectiveness of influenza vaccination recommendations in two cities that represent a broad latitudinal range in the tropical region of Brazil—Belém and São Paulo. To reach this end, the timing and strain of available vaccines were compared with the timing and strain of viral data obtained from constant surveillance and strain characterization of these areas between 1999 and 2007. By contrasting historic data against alternative hypothetical vaccination scenarios, the results showed that the best strategy would be to provide Brazil with Northern Hemisphere vaccine recommendations, rather than Southern Hemisphere recommendations, because the protection provided by this vaccine and the subsequent circulating strains more closely matched those areas using the former of the two vaccination calendars. Given that most of Brazil is located in the Southern Hemisphere, these results are surprising.

As informed by Dr. Wladimir J. Alonso, the corresponding author of the article, the paradox of such results may be due to the complexity of influenza circulation in tropical regions. These findings can stimulate future analyses of influenza data in other tropical regions in order to examine whether the patterns shown here are also observed on other continents. Regardless of what future findings from other geographical regions may reveal, the results reported here have already been used by the Brazilian Ministry of Health to inform a possible change in the country's influenza vaccination calendar.



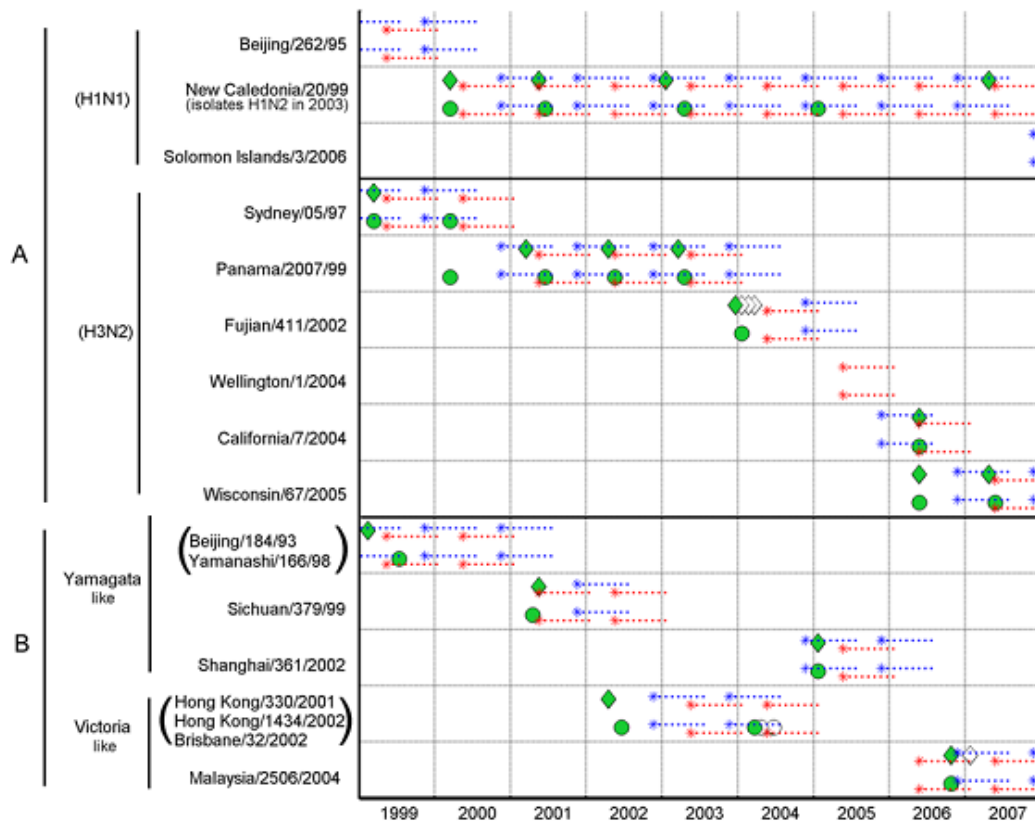


Figure 3. Matching success of vaccine strategies against strains of influenza viruses isolated monthly from 1999 to 2007 in Belém and São Paulo. The different categories of influenza strains considered in the study period are indicated on the vertical axis, sorted by influenza subtype (influenza A) and lineage (influenza B) and identification date. Time is measured on the horizontal axis. Strains isolated each month are represented by green diamonds for Belém, and green circles for São Paulo (blank symbols represent subsequent isolations of the same strain in the same season, and therefore were not considered for the analysis). Stars represent the first month of the period of vaccination-induced protection, while the following dotted lines represent the remaining months of protection. Red lines correspond to historical vaccination strategy adopted by the Brazilian authorities (i.e. relying on the southern hemisphere vaccine recommendations and schedule). Blue lines represent a hypothetical scenario whereby the northern hemisphere vaccination recommendations and schedule are used in both cities. The rate of successful matches between vaccines and circulating strains is quantified by the overlap between vaccine data (blue or red lines, depending on the scenario analyzed) and actual virus isolations (green circles and diamonds) through this period.

Recent MISMS Publications

For the full list of MISMS publications, visit <http://origem.info/FIC/Bibliography.html>

Influenza virus evolutionary patterns

- Lemey P, Suchard M, Rambaut A (Sep 2009) Reconstructing the initial global spread of a human influenza pandemic: A Bayesian spatial-temporal model for the global spread of H1N1pdm. PLoS Currents Influenza. RRN1031.
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- Rambaut A, Holmes E (Aug 2009) The early molecular epidemiology of the swine-origin A/H1N1 human influenza pandemic. PLoS Currents Influenza. RRN1003.



- Bahl J, Vijaykrishna D, Holmes EC, Smith GJ, Guan Y (Aug 2009) Gene flow and competitive exclusion of avian influenza A virus in natural reservoir hosts. *Virology*. 390(2): 289-97.
- Garten R, Davis C, Russell C, Shu B, Lindstrom S, Balish A, Sessions W, Xu X, Skepner E, Deyde V, Okomo-Adhiambo M, Gubareva L, Barnes J, Smith C, Emery S, Hillman M, Rivaller P, Smagala J, Miranda de Graaf, Burke D, Fouchier R, Pappas C, Alpuche-Aranda C, López-Gatell H, Olivera H, López I, Myers C, Faix D, Blair P, Yu C, Keene K, Dotson PD, Boxrud D, Sambol A, Abid S, St. George K, Bannerman T, Moore A, Stringer D, Blevins P, Demmler-Harrison G, Ginsberg M, Kriner P, Waterman S, Smole S, Guevara H, Belongia E, Clark P, Beatrice S, Donis R, Katz J, Finelli L, Bridges C, Shaw M, Jernigan D, Uyeki T, Smith D, Klimov A, Cox N (Jul 2009) Antigenic and Genetic Characteristics of Swine-Origin 2009 A(H1N1) Influenza Viruses Circulating in Humans. *Science*. 325(5937):197-201.
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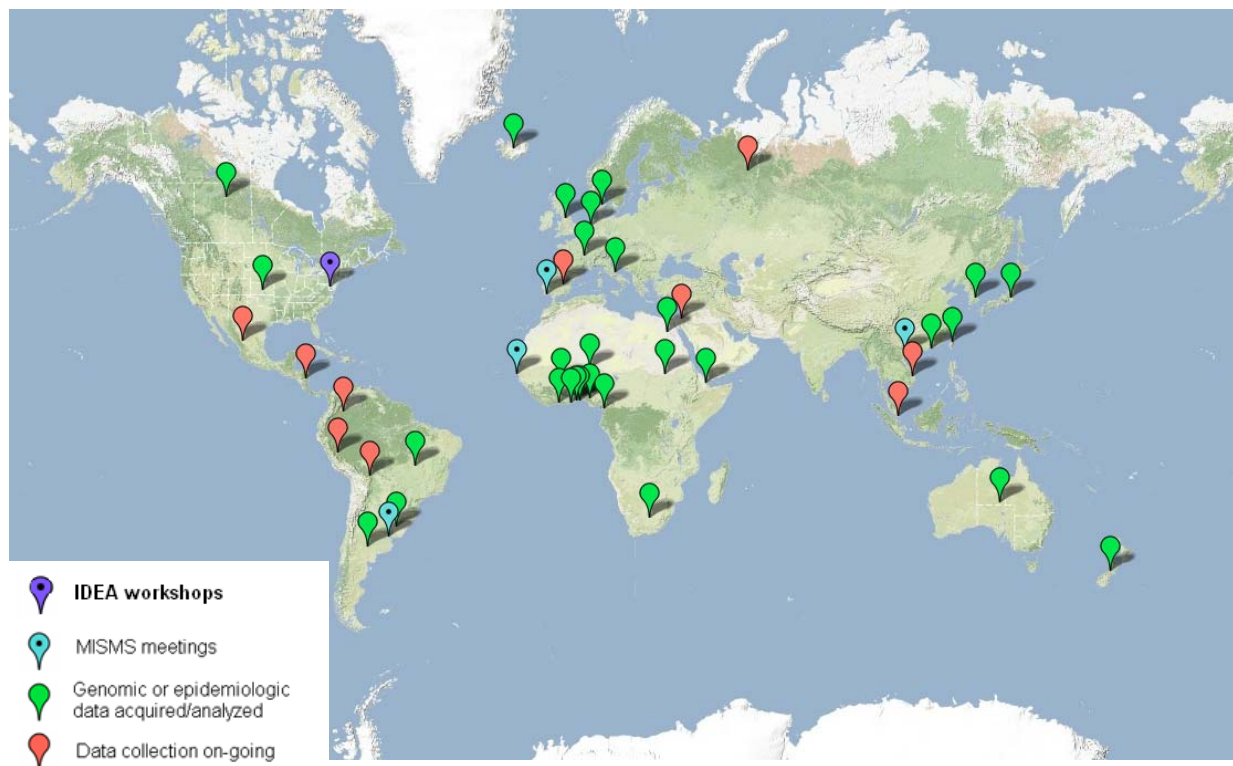
MISMS Overview

Originally called the Multinational Influenza Seasonal Mortality Study, MISMS was initiated in 2001 to analyze national and global mortality patterns associated with influenza virus circulation. The focus of MISMS has since expanded to include evaluating the interaction between the epidemiology, ecology, and evolutionary dynamics of influenza, including natural selection, reassortment, migration, and antigenic change.

MISMS has two specific aims:

1. To analyze the transmission patterns of influenza viruses, quantify time trends and geographical variations in age-specific disease burden, and evaluate control strategies.
2. To understand the interaction between the health impact and the antigenic, genomic, and evolutionary characteristics of influenza viruses in human, avian, and swine populations.

**Global of MISMS participation and regional meetings
(as of September 2009):**



For more information about MISMS, our publications, and our upcoming meetings, visit our website: <http://origem.info/misms/>

